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Proposed Registration Decision PRD2012-18

Fluroxypyr

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Overview

Proposed Registration Decision for Fluroxypyr

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Starane F Technical Herbicide and Starane II Herbicide, containing the active ingredient fluroxypyr, for postemergent suppression or control of kochia in industrial and non-cropland areas including roadsides, rights of way and industrial vegetation management areas.

Starane F Technical Herbicide (Registration Number 24814) and Starane II Herbicide (Registration Number 29463) are currently registered in Canada for use on spring and durum wheat, spring barley and oats, as well as on rangeland and permanent pasture. Industrial and non-cropland areas represent a major new use of the active ingredient fluroxypyr.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Starane F Technical Herbicide and Starane II Herbicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of the Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on fluroxypr, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on fluroxypyr, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Fluroxypyr?

Fluroxypyr is a systemic and selective post-emergent herbicide that offers control of hard-to-kill annual broadleaved weeds such as kochia (2-8 leaf), cleavers (1-4 whorl), and chickweed (up to 8 cm) in small grain cereals and control of kochia in rangeland, permanent pasture, industrial and other non-cropland areas. Fluroxypyr is formulated as fluroxypyr-methylheptyl ester which, after predominantly foliar uptake, hydrolyses to fluroxypyr acid, which is the herbicidally active form of fluroxypyr. Fluroxypyr induces auxin-type responses and disrupts plant cell growth in the newly forming stems and leaves of susceptible plants.

Health Considerations

Can Approved Uses of Fluoroxypyr Affect Human Health?

Fluroxypyr is unlikely to affect your health when used according to label directions.

Potential exposure to fluroxypyr may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, technical grade fluroxypyr (acid or methylheptyl ester) was of low acute toxicity by the oral and dermal routes and was of slight toxicity by the inhalation route of exposure. Fluroxypyr was mildly irritating to the eyes and non-irritating to the skin, and did not elicit an allergic skin reaction. Consequently, the hazard signal words "CAUTION – POISON – EYE IRRITANT" are required on the label.

The acute toxicity of the end-use product Starane II Herbicide was low via the oral, dermal and inhalation routes of exposure. It was moderately irritating to the eyes and mildly irritating to the skin. It caused an allergic skin reaction in mice. Consequently, the hazard signal words "WARNING – EYE AND SKIN IRRITANT - POTENTIAL SKIN SENSITIZER" are required on the label.

In animals given daily oral doses of fluroxypyr over long periods of time, decreases in body weight gain and changes to the kidneys and adrenals were observed. Fluroxypyr did not damage genetic material and did not cause tumours in rats or mice. There was no indication that fluroxypyr caused damage to the nervous system or immune system. Fluroxypyr did not cause birth defects in the developing young, or effects on the reproductive system. When fluroxypyr ester was given to pregnant animals, a foetal variation (retrocaval ureter) was noted in the absence of maternal toxicity, indicating that the young were more sensitive to fluroxypyr than the adult animals. The risk assessment protects against the effects of fluroxypyr by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Occupational Risks From Handling Starane II Herbicide

Occupational risks are not of concern when Starane II Herbicide is used according to the proposed label directions, which include protective measures.

Workers who mix, load or apply Starane II Herbicide, as well as field workers re-entering freshly treated non-crop areas, can come in direct contact with fluroxypyr residues on the skin. Mixers, loaders and applicators may also be exposed by breathing sprays and mists. Therefore, the label specifies that anyone mixing/loading and applying Starane II Herbicide must wear coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves. The label also requires that workers do not enter treated industrial and non-cropland areas until residues have dried. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals is not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Fluroxypyr Is Introduced Into the Environment?

Fluroxypyr in the form of fluroxypyr-methylheptyl ester is non-persistent in the environment and transforms readily to fluroxypyr acid. Fluroxypyr-methylheptyl ester is expected to impact terrestrial plants and aquatic organisms, therefore, spray buffer zones are required during application.

Fluroxypyr-methylheptyl ester will enter the environment through application to industrial and non-cropland areas. Fluroxypyr-methylheptyl ester is non-persistent in the environment and has low potential to leach. Fluroxypyr-methylheptyl ester biotransforms in soil and aquatic systems with hydrolysis as the predominant degradation mechanism. Fluroxypyr acid is slightly to moderately persistent in the environment and has moderate potential to leach. Phototransformation is not an important process for either of these chemicals. Two major biotransformation products of fluroxypyr-methylheptyl ester and fluroxypyr acid were identified: pyridinol, which is slightly to moderately persistent, and methoxypyridine, which is more persistent. These transformation products have mobility potential in soil but have low to moderate potential to leach to groundwater. In aquatic systems, fluroxypyr-methylheptyl ester partitions into the sediment phase after a few hours, then quickly hydrolyzes to its acid equivalent, fluroxypyr acid. Once fluroxypyr acid is released into the water phase it is expected to slowly transform under aerobic conditions. Fluroxypyr-methylheptyl ester or fluroxypyr acid will not bioconcentrate in fish.

Fluroxypyr is applied by broadcast sprayer. There is a potential that non-target terrestrial and aquatic habitats may be exposed to the chemical as a result of spray drift or runoff. Fluroxypyr-methylheptyl ester does not present a risk to earthworms, birds, small mammals, bees and beneficial arthropods. However, it poses a risk to non-target terrestrial plants and freshwater organisms including aquatic invertebrates, fish, amphibians and algae. Precautionary statements are included on the end-use product Starane II Herbicide label, and buffer zones of five metres (terrestrial habitats) and one metre (aquatic habitat) are required to mitigate risk to non-target plants and aquatic organisms from spray drift. Fluroxypyr acid does not pose a risk to terrestrial or aquatic non-target organisms.

Value Considerations

What Is the Value of Starane II Herbicide?

Starane II Herbicide is a post-emergent herbicide to control specific broadleaf weeds in small grain cereals, rangeland, permanent pasture, industrial and non-cropland areas.

Fluroxypyr formulated as Starane Herbicide (Registration Number 24815), was first registered in Canada in 1997 for control or suppression of cleavers, kochia (including Group 2 resistant biotype), round-leaved mallow, volunteer flax, chickweed, hempnettle, wild buckwheat, and stork's-bill in spring wheat, durum wheat, and spring barley.

Starane II Herbicide, with a higher product guarantee, was registered based on the registration of Starane Herbicide. Starane II Herbicide can be applied as a broadcast treatment at a rate of 0.21-0.41 L/ha in spring wheat, durum wheat, spring barley and oats. Starane II Herbicide may also be applied alone at a rate of 0.42 or 0.84 L/ha for suppression or control of kochia (including Group 2 resistant biotype), respectively, or in a tank mixture with Milestone Herbicide (Registration Number 28517; 240 g/L aminopyralid) at a rate of 0.25-0.5 L/ha for control of broad weed spectrum in industrial and other non-cropland areas.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Starane II Herbicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

To minimize direct contact with fluroxypyr residues on the skin, anyone mixing, loading and applying Starane II Herbicide must wear coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.

Workers must not enter treated industrial and non-cropland areas until residues have dried.

Environment

To mitigate risk to non-target terrestrial plants and aquatic organisms, buffer zones of five metres (terrestrial habitats) and one metre (aquatic habitats) are required during application.

Next Steps

Before making a final registration decision on fluroxypyr, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on fluroxypyr (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Fluroxypyr

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Common Names: Fluroxypyr-meptyl, Fluroxypyr-methylheptyl ester
CAS Name: 1-methylheptyl 2-[(4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy]acetate

1.2 Physical and Chemical Properties of the Active Ingredients and End-use Product

Technical Product—Starane F Technical Herbicide

Property	Result
Colour and physical state	Off-white solid
Nominal concentration	68% fluroxypyr (present as 1-methylheptyl ester)
Odour	Odourless
Density	1.2 g/mL
Vapour pressure at 20°C	1.349×10^{-3} mPa
pH	6.81 (0.009% w/w solution)
Solubility in water	0.09 mg/L
n-Octanol/water partition coefficient (K_{ow})	pH: 5, 7 log K_{ow}: 4.53, 5.04

End-use Product—Starane II Herbicide

Starane II Herbicide contains the active ingredient fluroxypyr (present as 1-methylheptyl ester) at a nominal concentration of 333 g/L. This product has a density of 1.0552 g/mL at 20°C and pH of 4.58. The chemistry requirements for Starane II Herbicide are complete.

1.3 Directions for Use

Starane II Herbicide is presently registered in Canada for application at a rate of 0.21-0.41 L/ha for post-emergent control of specific broadleaf weeds in spring wheat, durum wheat, spring barley and oats. In addition, the tank mixture of Starane II Herbicide at 0.42-0.84 L/ha + Milestone Herbicide (Registration Number 28517; 240 g/L aminopyralid) at 0.25-0.5 L/ha is used in rangeland and permanent pasture.

Starane II Herbicide is supported for application at a rate of 0.42 or 0.84 L/ha for post-emergent suppression or control of kochia (including Group 2 resistant biotype), respectively, in industrial and other non-cropland areas. For control of broad weed spectrum in these areas, Starane II Herbicide can be applied in a tank mixture with Milestone Herbicide at a rate of 0.25-0.5 L/ha.

For use in rangeland, permanent pasture, industrial and other non-cropland areas, Starane II Herbicide can be applied as a broadcast spray or an individual plant or spot/strip spray. For individual plant or spot/strip spray, Starane II Herbicide should be applied thoroughly and uniformly to cover the foliage of target plants but not to the point of runoff.

1.4 Mode of Action

Fluroxypyr is formulated as fluroxypyr-methylheptyl ester in the end use product Starane II Herbicide which, after predominantly foliar uptake, hydrolyses to fluroxypyr acid, which is the herbicidal active form, and translocates rapidly to other parts of the plants. It accumulates in growing tissues to higher concentrations than the native auxin does, and degrades more slowly. Plant growth is disrupted by the deregulation of cellular growth process following binding of fluroxypyr to plant cell auxin receptor sites. Fluroxypyr also interferes with the plant's ability to metabolize nitrogen and produce enzymes. When growth regulation of plants is disrupted in this fashion, plant growth becomes disorganized and results in plant death. Fluroxypyr is classified as a Group 4 Herbicide by the Weed Science Society of America.

2.0 Methods of Analysis

The methods provided for the analysis of the active ingredient and the impurities in Starane F Technical Herbicide have been validated and assessed to be acceptable for the determinations. The method provided for the analysis of the active ingredient in Starane II Herbicide has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Fluroxypyr-methylheptyl ester was employed as the technical grade active ingredient in Starane F Technical and the end-use product Starane II Herbicide. Fluroxypyr-methylheptyl ester is rapidly and completely hydrolysed *in vivo* to fluroxypyr acid, which is the active herbicide. Both forms of fluroxypyr are considered toxicologically equivalent.

A detailed review of the toxicological database for fluroxypyr was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices (GLP). The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to fluroxypyr. The database contains studies for both forms of fluroxypyr for a majority of required studies including toxicokinetics, teratogenicity and genotoxicity studies.

The technical grade active ingredient fluroxypyr ester and the acid form were of low acute toxicity by the oral route of exposure in rats and by the dermal route of exposure in rats and rabbits. Fluroxypyr ester and the acid form were slightly toxic by the inhalation route in rats. They were mildly irritating to the eyes and non-irritating to the skin of rabbits. Fluroxypyr ester and the acid form were not dermal sensitizers in guinea pigs.

Starane II Herbicide was of low acute toxicity by the oral, dermal and inhalation routes of exposure in rats. It was moderately irritating to the eyes and mildly irritating to the skin of rabbits. Starane II Herbicide was a potential skin sensitizer in mice.

Metabolism studies with the acid or ester forms of radiolabelled fluroxypyr (pyridyl ring) in rats showed rapid absorption and complete elimination of the test compound. Plasma peak concentrations were attained in 30 minutes at the low dose (LD) and 1.5 hours at the high dose (HD). Saturation of absorption occurred at the HD. Repeated dosing produced similar results. There were no significant differences between sexes. Fluroxypyr-methylheptyl ester was rapidly hydrolysed and excreted in urine (~94%) and feces (~6%) as the acid. The hydrolysis of the ester bond was the only significant biotransformation, fluroxypyr acid accounting for >93% of the urinary excreted radioactivity, while a less polar component accounted for 1-2% of administered dose, with other radioactive components being present at less than 1%. Negligible amounts were detected via biliary excretion (<1%) and no radioactivity was detected in the expired air (at 48 hours). Autoradiography showed a wide distribution of the radiolabelled compound with highest concentrations being in the GI tract, kidneys and urinary tract. Fluroxypyr is a weak acid and was likely actively secreted in the proximal tubules of the kidneys, hence the fast elimination in urine and the specific toxicity observed in longer term studies. The HD did not achieve saturation of elimination. Ninety-eight percent of the radiolabelled fluroxypyr was eliminated in urine within 12 hours after dosing and 94% after 48 hours. There is no potential for bioaccumulation.

Additional publicly available information on the metabolism of the methylheptyl portion (outside the pyridyl ring) indicated that the ester bond of fluroxypyr-methylheptyl ester (radiolabelled as fluroxypyr 1-methylheptyl-1-^{14}C-ester) was rapidly hydrolysed and the radiolabelled portion behaved like methylheptanol and was determined to be bioequivalent. Both were extensively metabolised (~ 20 metabolites) and mainly eliminated at similar rates and proportions in expired air (~61-63%), urine (~30-27%) and feces (~5-7%).

After 21-days of dermal dosing with fluroxypyr in rabbits, no treatment-related effects were observed at any of the doses tested, up to the limit dose.

After repeated oral dosing, the kidneys were the primary target in all species tested. In mice, rats and dogs, the key treatment-related effects were tubular dilation and cellular irregularity, papillary interstitial hypercellularity, cellular atrophy progressing to tubular degeneration, papillary necrosis and general kidney nephrosis confirmed by histological and clinical chemistry findings. The adverse kidney effects were observed in mice, rats and dogs at similar doses. Male rats were more sensitive than female rats to kidney effects. While the adverse effects in the kidneys were seen in all of the species tested, urothelial hyperplasia of the kidney pelvis, hypertrophy and/or degeneration of the adrenal zona glomerulosa, depletion of the red and white splenic pulp, involution of the thymus and atrophy of the seminal vesicles were seen only in the rat short-term studies at higher doses than those used in longer term studies.

Fluroxypyr did not demonstrate genotoxic potential when tested in a battery of in vitro and in vivo genotoxicity assays including reverse mutation assay, gene mutation assay, chromosomal aberration assay, micronucleus assay and unscheduled DNA synthesis.

In an oral 18-month mouse oncogenicity study and in two oral 2-year chronic/oncogenicity studies in rats, the same kidney effects observed previously in the short-term studies were observed, with severity increasing over time. The effects observed in rats included increased kidney weight, papillary necrosis, pelvic epithelial hyperplasia and tubular nephrosis with greater sensitivity in the male rats. There was increased mortality in male rats, mainly due to kidney failure.

With respect to oncogenicity, fluroxypyr did not cause an increased incidence of tumours in either mouse or two rat oncogenicity studies, up to the limit dose.

In a 2-generation reproductive toxicity study in rats, no treatment-related effects were observed in parental animals or offspring. There was no evidence of reproductive toxicity. Dosing was considered adequate based on the results of other studies.

In rat developmental toxicity studies, the dams showed increased kidney weights, increased incidence of renal dilation and decreased body weights, body weight gains and food consumption. There were mortalities in dams at the LOAEL preceded by agonal signs of death. Developmental toxicity was observed at maternally toxic levels and included reduced ossification of sternabrae, incomplete ossification of cervical vertebral transverse processes and incompletely ossified pubes in the foetus. There was no evidence of malformations and there was no sensitivity of the young.

In rabbit developmental toxicity studies, maternal toxicity was observed at the high dose as body and kidney weight effects (acid study) and abortions (ester study) during the last week of pregnancy. In both studies, foetal effects were observed. In the acid study, increased early resorptions and post implantation losses were observed in the presence of maternal toxicity (body and kidney weight effects). These effects were considered equivocal because of the significant variability of the data and the fact that the exclusion of a statistical outlier would bring the data into the historical control range. In the ester study, an increased incidence of retrocaval ureter was observed in the absence of maternal toxicity. This congenital structural

change is subject to debate within the scientific community regarding its classification as a variation or a malformation. This change is the result of an abnormal process, but is unlikely to adversely affect health of the animal (Solecki *et al.*, 2003). In humans, retrocaval ureter has a prevalence of 0.1% of births with a male:female ratio of 3:1. It usually remains asymptomatic until the third or fourth decade of life and often requires surgery to correct the anomaly. As per recommendations of the Fourth Workshop on the Terminology in Developmental Toxicology held in Berlin (Solecki *et al.*, 2003) to address the issues raised by ambiguous terminology, retrocaval ureter classification should be based on the available historical control data. In the case of fluroxypyr, the historical controls provided by the applicant support the spontaneous nature of this anomaly as the incidence in control animals was high, a feature of variations. Overall, the weight of evidence in this case indicates that retrocaval ureter should be considered as a variation. Consequently, fluroxypyr was not considered teratogenic but foetal sensitivity was observed.

Considering the entire database, fluroxypyr did not present a potential for neurotoxicity.

Results of the toxicology studies conducted on laboratory animals with fluroxypyr and its associated end-use product are summarized in Tables 1 and 2 of Appendix I. The toxicology endpoints for use in the human health risk assessment are summarized in Table 3 of Appendix I.

3.1.1 Pest Control Products Act Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the full complement of required studies including two developmental toxicity studies with the acid and ester forms in both rats and rabbits and a reproductive toxicity study in rats with the acid form.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of foetuses or offspring compared to parental animals in the rat reproductive and developmental toxicity studies. Minor developmental effects (increased incidence of skeletal variations) were observed in the rat; however, these effects occurred in the presence of maternal toxicity. There was an indication of increased susceptibility of foetuses compared to parental animals in the rabbit developmental toxicity study performed with the ester form. A developmental variation (retrocaval ureter) was observed in the absence of maternal toxicity. The seriousness of this finding was tempered by the high incidence of this variation in the historical controls and by the fact that the effect observed was just slightly over the historical control values.

Overall, endpoints in the young were well-characterized and not considered serious in nature. On the basis of this information, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Determination of Acute Reference Dose

No acute toxicity endpoint was identified.

3.3 Determination of Acceptable Daily Intake

To estimate dietary risk from repeat exposure, the 2-year oral chronic/oncogenicity study in rats with a NOAEL of 100 mg/kg bw/day was selected for risk assessment. At the LOAEL of 500 mg/kg bw/day, kidney nephrosis was observed. The NOAEL selected is considered to be protective of the effects observed in the database after repeated administration of fluroxypyr. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{100 \text{ mg/kg bw/day}}{100} = 1 \text{ mg/kg bw/day of fluroxypyr}$$

The ADI provides a margin of 100 to the dose at which variations were observed in rabbits.

Cancer Assessment
There was no evidence of oncogenicity in the database, therefore no cancer risk assessment was required.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to fluroxypyr is characterized as being of short-term duration and is predominantly by the dermal and inhalation route for mixer/loader/applicators, and by the dermal route for workers re-entering treated areas

Short- and intermediate-term inhalation
For short-, and intermediate-term inhalation risk assessment, the 2-year oral chronic toxicity / oncogenicity study in rats was selected since an appropriate inhalation study was not available. At the LOAEL of 500 mg/kg bw/day, kidney nephrosis was observed in males. A NOAEL of 100 mg/kg bw/day was established. The target margin of exposure for this endpoint is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability.

Short- and intermediate-term dermal
For short-, and intermediate-term dermal risk assessment, the 21-day dermal study in rabbits was selected as an appropriate study. In absence of adverse effects at the highest dose tested, a NOAEL was established at 1000 mg/kg bw/day. The target margin of exposure for this endpoint is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability

3.4.1.1 Dermal Absorption

Dermal absorption data were not submitted for fluroxypyr. In addition, a dermal absorption factor is not required, since the toxicological endpoint relevant to dermal occupational exposure is based on a short-term dermal toxicity study.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/Loader/Applicator Exposure and Risk Assessment

Individuals have potential for exposure to fluroxypyr during mixing, loading and application. Exposure to workers mixing, loading and applying Starane II Herbicide is expected to be short-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixer/loaders/applicators applying Starane II Herbicide using broadcast sprayers and handheld equipment such as low pressure handwand, backpack sprayer and high pressure handwand. The exposure estimates are based on mixers/loaders/applicators wearing coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.

As chemical-specific data for assessing human exposures were not submitted, dermal and inhalation exposures for workers were estimated using the Pesticide Handlers Exposure Database (PHED) Version 1.1. PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (no observed adverse effects levels [NOAELs]) to obtain the margin of exposure (MOE); the target MOE is 100. PHED unit exposure values and estimates of exposure and risk are presented in Appendix I, Tables 4 and 5, respectively, for Starane II Herbicide. Acceptable MOEs were calculated for workers who wear the personal protective equipment stated on the product label.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with Starane II Herbicide during scouting, mechanical weeding and mowing. The duration of exposure is considered to be short-term for all re-entry activities. The primary route of exposure for workers re-entering treated areas would be through the dermal route. Inhalation exposure is not considered to be a significant route of exposure for people entering treated areas compared to the dermal route, since fluroxypyr is relatively non-volatile (4.66×10^{-6} Pa) and as such, a risk assessment was not required.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients. Chemical-specific dislodgeable foliar residue data were not submitted. As such, a default dislodgeable foliar residue value (DFR) of 20% of the application rate was used in the exposure assessment.

The exposure estimate was compared to the toxicological endpoint (NOAEL = 1000 mg/kg bw/day) to obtain the MOE; the target MOE is 100. Since this value exceeds the target MOE of 100 (Appendix I, Table 6), this level of postapplication exposure is not a health concern. As such, a required restricted entry interval (REI) of "until residues are dried" for non-crop uses is adequate.

3.4.3 Residential Exposure and Risk Assessment

There are no residential uses for Starane II Herbicide and as such, a residential risk assessment was not required. Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to when there is low risk of drift to areas of human habitation such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings

3.5 Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the PMRA website. Incidents from Canada and the United States were searched and reviewed for fluroxypyr, and any additional information submitted by the applicant during the review process was considered.

As of 23 March, 2012, there have been four human incidents reported for products containing fluroxypyr in Canada (three) and the United States (one) which were classified as moderate to major; most involved occupational (applicator) exposure. All of the pesticide products concerned in these incidents contained at least one other technical grade active ingredient. The effects reported were respiratory symptoms with mucous membrane irritation, tachycardia and lethargy. In two cases, there was either no exposure to the product (packaging failure) or the relationship to the pesticide product was scientifically implausible. The other incidents resulted from an accidental spill (oral and skin exposure) or the repeated use of a malfunctioning applicator device.

The PMRA concluded that the information from the incident reports was consistent with the current toxicity database for fluroxypyr; however, it did not impact upon the risk assessment for Starane F Technical Herbicide. Further information on the incidents can be found on the PMRA Public Registry

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Fluroxypyr-methylheptyl ester is sparingly soluble in water (0.109 mg/L) and is slightly volatile from water surfaces and moist soils (Henry's law constant = 1.55×10^{-7} atm m^3 /mole). On the basis of its UV-visible absorption spectrum (λ_{max}=210 nm), it is not expected to phototransform in water or on soil under natural light.

Fluroxypyr acid is very soluble in water (7950 mg/L) and is non-volatile from water surfaces and moist soils (Henry's law constant = 3.42×10^{-15} atm m^3 /mole). Fluroxypyr acid is not expected to phototransform in water under natural light (λ_{max}=210 nm).

The octanol-water partition coefficient (log K_{ow} = 4.53–5.31) for fluroxypyr-methylheptyl ester indicated a potential to bioaccumulate. However, a fish bioaccumulation study reporting a bioconcentration factor (BCF) of 26 for fluroxypyr-methylheptyl ester, suggests that this compound is not expected to bioaccumulate in aquatic biota.

Abiotic hydrolysis of fluroxypyr-methylheptyl ester is dependent on temperature, pH and concentration in water. At 25°C, fluroxypyr-methylheptyl ester quickly hydrolyzed in alkaline solution (pH 9) while, under acidic and neutral conditions (pH 5-7), it was stable. In highly diluted solutions, fluroxypyr-methylheptyl ester hydrolysed rapidly, regardless of the solution's pH, with a half-life of less than one day. Fluroxypyr acid is stable to hydrolysis (pH 5-9).

In soils, biotransformation was the major route of dissipation of fluroxypyr-methylheptyl ester with hydrolysis (abiotic and microbially-mediated) as a predominant degradation mechanism. Fluroxypyr-methylheptyl ester quickly biotransformed to fluroxypyr acid ($t_{1/2}$ < 2 days) through hydrolysis. Fluroxypyr acid then biotransformed to pyridinol and methoxypyridine, the two major transformation products in soil. Both transformation products further transformed to CO_2 and non-extractable residues Fluroxypyr acid is non-persistent to moderately persistent in

aerobic soils under laboratory conditions. Based on terrestrial field dissipation studies, fluroxypyr-methylheptyl ester, fluroxypyr acid and pyridinol are not persistent. Methoxypyridine, however, may carry over into the next growing season, but this is not expected to be a concern to the environment. The rate of biotransformation of fluroxypyr-methylheptyl ester under anaerobic conditions in laboratory studies was similar to that under aerobic conditions whereas fluroxypyr acid was more persistent. An assessment of leaching potential based on results of laboratory and field dissipation studies, as well as the groundwater ubiquity score (GUS) and physical properties indicated that fluroxypyr-methylheptyl ester had low mobility in soil and had low potential to leach to groundwater. Fluroxypyr acid, pyridinol and methoxypyridine were of low to moderate mobility in soil and had moderate to high potential to leach to groundwater. This was also confirmed by results from drinking water modelling. Field studies indicated that the potential for groundwater contamination by transformation products of fluroxypyr-methylheptyl ester was expected to be limited.

In water/sediment systems, biotransformation was the major route of dissipation of fluroxypyr_ethylheptyl ester, with hydrolysis as the predominant degradation mechanism. Fluroxypyr-methylheptyl ester partitioned into sediment (up to 50% of applied), after two hours, and was quickly hydrolyzed and released to the aquatic phase as fluroxypyr acid. Under aerobic aquatic conditions, in laboratoty studies, fluroxypyr-methylheptyl ester and fluroxypyr acid were non-persistent to slightly persistent as the estimated whole system $t_{1/2}$ values were 7.0-38.1 days. Major transformation products included the dichloropyridinol, dichloropyridinone and 3-hloropyridinol derivatives. Fluroxypyr-methylheptyl ester was also non-persistent under anaerobic aquatic conditions.

Data on the environmental fate and behaviour of fluroxypyr-methylheptyl ester, fluroxypyr acid and their transformation products are summarized in Appendix I, Table 8.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC).

If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

A summary of terrestrial organisms' toxicity data for fluroxypyr-methylheptyl ester, fluroxypyr acid and their transformation products is presented in Appendix I, Table 9. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with fluroxypyr-ethylheptyl ester. A summary of endpoints used in risk assessment is presented in Appendix I, Table 11.

Earthworms

Fluroxypyr-methylheptyl ester is not acutely toxic to earthworms up to the highest concentration tested (1000 mg a.i./kg soil). Earthworm (*Eisenia fetida*) survival was adversely affected by fluroxypyr-acid (LC_{50} = 64.8 mg a.e./kg dry soil), pyridinol (LC_{50} = 79 mg/kg dry soil) and methoxypyridine (LC_{50} = 313 mg/kg dry soil). The screening level risk assessment was conducted based on the EECs for the highest use rate scenario for fluroxypyr in Starane II Herbicide on rights-of way, industrial and non-crop areas (404 g a.i./ha). The LOC was not exceeded for earthworms (Appendix I, Table 12) for any of the chemicals.

Bees (pollinators) and beneficial arthropods

No adverse effects were observed when bees were exposed to fluroxypyr-methylheptyl ester on an acute oral or contact basis (LD_{50} > 100 µg a.i./bee). Bee survival was adversely affected by fluroxypyr acid on an acute oral basis (LD_{50} = 37.1 µg a.e./bee), but not on acute contact basis (LD_{50} > 180 µg a.e./bee). No mortality or adverse effects were observed when the predatory mite (*Typhlodromus pyri*) was exposed to Starane 180 EC (Registration Number 24815; 180 g/L fluroxypyr) on glass plates (LR_{50} > 570 g a.i./ha). Mortality was observed when the parasitic wasp (*Aphidius rhopalosiphi*) was exposed to Starane 180 EC on glass plates (LR_{50} = 337 g a.i./ha). The screening level risk assessment was determined based on the

maximum application rate of 404 g a.i./ha or 280 g a.e./ha. The LOC was not exceeded for bees, predatory mite and parasitic wasp (Appendix I, Table 12). Pollinators and beneficial arthropods are, thus, not expected to be at risk from the application of fluroxypyr from the Canadian use pattern.

Non-target plants

The effect of fluroxypyr-methylheptyl ester (99.5% guarantee) to non-target plants was determined through exposure to standard crop species. Multiple toxicity end-points were generated and the hazardous concentration to 5% of the species (HC_5) was then calculated using species sensitivity distributions (SSDs) models. The HC_5 for post-emergence phytotoxicity was used in screening level risk assessment based on EECs from the direct application of fluroxypyr-methylheptyl ester at the maximum application rate of 404 g a.i./ha or 280 g a.e./ha. The screening level risk assessment shows that the LOC was exceeded for terrestrial plants (Appendix I, Table12). A refined Tier I assessment was conducted based on drift of fluroxypyr-methylheptyl ester on non-target plants located one metre downwind from the point of application. The LOC was still exceeded for terrestrial plants (Appendix I, Table 15). Non-target plants are, thus, expected to be at risk from the use of fluroxypyr-methylheptyl ester from the Canadian use pattern. Spray buffer zones will be required on the label to protect non-target terrestrial vascular plants.

Birds and small wild mammals

No treatment-related mortalities or clinical effects were observed in the acute oral and dietary exposure of fluroxypyr-methylheptyl ester and fluroxypyr acid to bobwhite quail (*Colinus virginianus*) and mallard duck (*Anas platyrhynchos*). No reproductive adverse effects on bobwhite quail and mallard ducks were observed at a concentration of 500 mg a.i./kg diet.

Fluroxypyr-methylheptyl ester and fluroxypyr acid were reported to be of low toxicity to the rat with $LD_{50} > 2000$ mg a.i./kg bw/day, on an acute oral basis (for fluroxypyr-methylheptyl ester) and a NOAEL of 250 mg a.e./kg bw/day on a chronic (teratogenicity) basis (for fluroxypyr acid). The clinical symptoms in dosed rats included piloerection and listlessness, shortly after administration of fluroxypyr-methylheptyl ester, but were reversible within 24 hours.

The screening level risk assessment was performed based on EECs from the maximum application rate (404 g a.i./ha) on rights-of way, industrial and non-crop area. The LOC was not exceeded for birds and mammals on acute and chronic basis; therefore, a risk to birds and small wild mammals as a result of the proposed use of fluroxypyr is not expected. The results of the risk assessment are presented in Appendix I (Table 13 and 14).

4.2.2 Risks to Aquatic Organisms

A summary of the freshwater and marine/estuarine toxicity data for fluroxypyr-methylheptyl ester, fluroxypyr acid and their transformation products is presented in Appendix I, Table 10. For the assessment of risk, toxicity endpoints from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with fluroxypyr (Appendix I, Table 11). The potential exposure of fluroxypyr-methylheptyl ester, fluroxypyr acid

and transformation products to the aquatic environment was assessed based on screening level EECs from the direct application of fluroxypyr-methylheptyl ester (404 g a.i./ha) to water bodies of two different depths (80 cm and 15 cm). The 80 cm deep water body was chosen to represent a permanent body of water and 15 cm deep was chosen to represent a seasonal body of water. The result of the screening level risk assessment for aquatic organisms is presented in Appendix I, Table 12.

Freshwater invertebrates

Fluroxypyr-methylheptyl ester was not toxic to *Daphnia magna* on an acute basis up to the limit of solubility of the compound (LC_{50} > 0.2 mg a.i./L). Fluroxypyr acid and pyridinol were slightly toxic to *Daphnia magna* on an acute basis. Fluroxypyr-methylheptyl ester was also more toxic to *Daphnia magna* than fluroxypyr acid and pyridinol on a chronic basis. The screening level risk assessment shows that the LOC was not exceeded for either acute or chronic exposure to freshwater invertebrates. No acute or chronic toxicity data were available for methoxypyridine. The results of the risk assessment are presented in Appendix I, Table 12.

Freshwater fish and amphibians

Fluroxypyr-methylheptyl ester was not toxic to rainbow trout on an acute basis up to the limit of solubility of the compound (LC_{50} > 0.2 mg a.i./L). Fluroxypyr acid and pyridinol were slightly toxic to bluegill sunfish and rainbow trout on an acute basis. However, fluroxypyr-methylheptyl ester was more toxic to rainbow trout than fluroxypyr acid on a chronic basis. The screening level risk assessment indicated that the LOC was exceeded for acute, but not for chronic exposure of fluroxypyr-methylheptyl ester to freshwater fish. The LOC was not exceeded for either acute or chronic exposure of fluroxypyr acid to freshwater fish. The risk quotient from the refined Tier I risk assessment for fish indicated that the LOC was not exceeded for the acute exposure to fluroxypyr-methylheptyl ester through spray drift. A refined Tier I assessment based on run-off of fluroxypyr-methylheptyl ester into the receiving water body was not conducted as this product is non-persistent and is expected to rapidly hydrolyze into its less toxic acid equivalent (fluroxypyr acid) in soil and water. The results of the risk assessment are presented in Appendix I, Table 12.

The risk to aquatic life stages of amphibians was assessed by comparing EECs in 15 cm water depth with fish toxicity endpoints values as surrogate endpoints. The amphibian screening level risk quotients for both acute and chronic exposure to fluroxypyr-methylheptyl ester exceeded the LOC (Appendix I, Table 12). The risk quotients from the refined Tier I risk assessment for amphibians, marginally exceeded the LOC for the acute exposure (RQ < 1.2) when considering exposure from spray drift through ground application (Appendix I, Table 15). No-spray buffer zones will be required on the label to protect non-target aquatic organisms.

Freshwater or marine/estuarine plant species
Fluroxypyr-methylheptyl ester, fluroxypyr acid, pyridinol and methoxypyridine were toxic the freshwater algae (green and blue green algae), vascular plants (*Lemna gibba*) and marine diatom (*Skeletonema costatum*) in the range of concentrations tested. The screening level LOC was exceeded for the freshwater algae *Navicula pelliculosa* exposed to fluroxypyr-methylheptyl ester (Appendix I, Table 12). However, the risk quotient from the refined Tier I risk assessment for freshwater indicated that the LOC was not exceeded for fluroxypyr-methylheptyl ester for spray drift. The results of the risk assessment are presented in Appendix I, Table 15.

4.2.3 Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the PMRA website. Incidents from Canada and the United States were searched and reviewed for fluroxypyr.

As of 23 May, 2012, the PMRA is not aware of any Canadian incident reports related to adverse effects on wildlife or natural vegetation from fluroxypyr. However one incident is reported in the USEPA's Ecological Incident Information System (EIIS). The incident was listed as probable and involved damage to 18.6 ha of field corn in Buffalo County in 2004. The evening following chemical application, the wind picked up to 96.5 km/hour gusts which snapped off an estimated 60% of the corn. It is reported that the corn field being settled on was a Mycogen conventional hybrid (2R773) which is sensitive to plant growth regulators (PGRs). The corn which was still standing showed very clear signs of PGR damage. By using county data, it was estimated that the 2004 yields were on average down 6% in the given area.

The PMRA concluded that the information from the incident reports was consistent with the known toxicity hazard of fluroxypyr to plants

5.0 Value

5.1 Effectiveness against Kochia in Industrial and Other Non-crop Areas

Efficacy data from a total of 13 field trials conducted in Canada and US over five years were submitted. The trials were conducted in grassland (non-cultivated), industrial sites, ditch banks, road sites, or summer fallow. Each trial was designed as randomized complete blocks (RCB) with three or four replicates. Herbicide treatments were applied with a backpack or tractor mounted sprayer using CO_2 or compressed air as a propellant. All sprayers delivered a uniform spray pattern that provided thorough coverage of the foliage. Herbicide treatments were applied post-emergence in the spring (May or June) to kochia at the 6- to 9-leaf stage or 10 to 75 cm in height; kochia densities were reported in five trials and ranged from 50 to 300 plants/m^2.

Kochia control was visually assessed on three occasions and reported as a percentage (%) compared to an untreated weedy control.

5.1.1 Acceptable Efficacy Claim for Starane II Herbicide as an Alone Treatment

Efficacy of Starane II Herbicide at 0.42 L/ha for kochia control was evaluated in 11 trials; mean kochia control was 59.5% at 8-20 days after treatment (DAT), 69.1% at 28-42 DAT, and 70.5% at 48-95 DAT. Efficacy data also demonstrated that the rate of 0.42 L/ha of Starane II Herbicide is the lowest effective rate for kochia suppression in industrial and other non-crop areas, where there is no sufficient host crop competition to assist in controlling kochia. The suppression claim for kochia at the rate of 0.42 L/ha of Starane II Herbicide in industrial and other non-crop areas is supported.

Efficacy of Starane II Herbicide at 0.84 L/ha for kochia control was evaluated in eight trials; mean kochia control was 70.8% at 8-20 DAT, 81.1% at 28-42 DAT, and 83.9% at 48-95 DAT. The control claim for kochia at the rate of 0.84 L/ha of Starane II Herbicide in industrial and other non-crop areas is supported.

5.1.2 Acceptable Efficacy Claim for Starane II Herbicide in a Tank Mixture with Milestone Herbicide

Tank mixture of Starane II Herbicide at 0.42 or 0.84 L/ha + Milestone Herbicide (Registration Number 28517; 240 g/L aminopyralid) at 0.25-0.5 L/ha is supported for use in industrial and other non-crop areas for the following reasons.

- A tank mixture of DE-750 Herbicide (Registration Number 28522; 240 g/L aminopyralid) + Starane Herbicide (Registration Number 24845; 180 g/L fluroxypyr) is presently labelled for control of broadleaf weeds in spring and durum wheat;

- The agronomic equivalence of DE-750 Herbicide to Milestone Herbicide and Starane Herbicide to Starane II Herbicide was previously determined;

- The application rate of Starane II Herbicide of 0.42 or 0.84 L/ha is supported for kochia control in industrial and other non-crop areas and the application rate of Milestone Herbicide of 0.25-0.50 L/ha is currently registered.

5.2 Phytotoxicity to Host Plant

As primarily permanent perennial grass covers some industrial and other non-crop areas (for example, roadside, rights-of-way, etc.), tolerance of grasses to Starane II Herbicide at up to 280 g a.i./ha was assessed.

Data previously submitted from a total of 42 field trials demonstrated that tall fescue, creeping red fescue, intermediate wheatgrass, crested wheatgrass, meadow brome grass, smooth brome grass, and timothy exhibited an adequate margin of crop safety to fluroxypyr at up to 284 g a.i./ha. Therefore, application of fluroxypyr at up to 280 g a.i./ha on permanent perennial grasses is supported as per label instruction.

5.3 Product Regional Restriction

Efficacy trials submitted were conducted in various locations in Canada and the US, which are representative of Western and Eastern Canada determining by crop zone. For instance, five trials were conducted within Crop Zone 5, which is the same zone as Ontario, and three trials were conducted within Crop Zone 11, which is the same zone as the interior region of British Columbia. The nation wide application of Starane II Herbicide for suppression or control of kochia in industrial and other non-crop areas is supported.

5.4 Impact on Succeeding Crops

Not applicable since there is no plant-back or rotational crop in uncultivated grassland, industrial sites, and other non-crop land.

5.5 Economics

Not available.

5.6 Sustainability

5.6.1 Survey of Alternatives

There are a few alternative herbicides presently registered for control of kochia (including Group 2 resistant biotypes) in industrial and other non-crop areas; such products include 2,4-D and MCPA. The registration of Starane II Herbicide in these areas provides an effective tool for control of Group 2 resistant kochia.

5.6.2 Compatibility With Current Management Practices Including Integrated Pest Management

Application of Starane II Herbicide would not exclude the sequential use of other herbicides with different modes of action for control of annual and perennial species not controlled by the product alone or when tankmixed.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, fluroxypyr-methylheptyl ester, fluroxypyr acid and their transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Fluroxypyr-methylheptyl ester and fluroxypyr acid do not meet Track 1 criteria, and are not considered Track 1 substances. See Appendix I, Table 7, for comparison with Track 1 criteria.

- Limited data were available to assess the TSMP Track 1 criteria for major transformation products of fluroxypyr-methylheptyl ester and fluroxypyr acid.

- Methoxypyridine meets the criteria for persistence in soil, with an estimated half-life range from 16.7 to > 1000 days. Half-lives in water or sediment could not be calculated as the compound was not found in aquatic systems. The log *n*-octanol–water partition coefficient (log K_{ow}) for methoxypyridine was determined to be 3.09, which is below the TSMP criteria for bioaccumulation.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade Starane F Technical Herbicide (containing fluroxypyr-methylheptyl ester) does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

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5 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

8 DIR2006-02, *PMRA Formulants Policy.*

- The end-use product, Starane II Herbicide, does not contain any formulants of health or environmental concern identified in the *Canada Gazette*. However, this end-use product does contain an aromatic petroleum distillate. Therefore, the label for Starane II Herbicide will include the statement: "This product contains aromatic petroleum distillates that are toxic to aquatic organisms."

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for fluroxypyr is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of oncogenicity in rats or mice after long-term dosing. Fluroxypyr was not genotoxic. There was no evidence of increased susceptibility of the young in reproduction or rat developmental toxicity studies. There was increased susceptibility of the foetus in the rabbit developmental study, however, the effect was not considered serious in nature. Fluroxypyr did not appear to be neurotoxic. In short-term and chronic studies in laboratory animals, the primary target was the kidney. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixer, loader applicators handling Starane II Herbicide and workers re-entering treated non-crop areas are not expected to be exposed to levels of fluroxypyr that will result in risks of concern when Starane II Herbicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers

7.2 Environmental Risk

Fluroxypyr-methylheptyl ester is non-persistent to slightly persistent in soils and aquatic systems. Fluroxypyr-methylheptyl ester has low potential to leach into ground water. Fluroxypyr acid is slightly to moderately persistent in the environment. The potential for groundwater contamination by fluroxypyr acid is expected to be limited due to rapid biotransformation processes. The risk assessment indicates that fluroxypyr-methylheptyl ester will pose a risk to non-target aquatic organisms and terrestrial plants. Risks to these organisms can be mitigated with precautionary label statements and no-spray buffer zones (five metres for terrestrial habitats and one meter for aquatic habitats) to protect sensitive terrestrial and aquatic habitats from spray drift.

7.3 Value

The value data submitted supported the registered Starane II Herbicide for kochia control in industrial and other non-crop areas when applied according to the label directions.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Starane F Technical Herbicide and Starane II Herbicide, containing the active ingredient fluroxypyr, to postemergent suppression or control of kochia in non-cropland areas including roadsides, rights of way and industrial vegetation management areas.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

♂ and ♀	male and female gender symbols
°C	degree(s) Celsius
a.e.	acid equivalent
a.i.	active ingredient
abs	absolute
ADI	acceptable daily intake
ALP	alkaline phosphatase
ARfD	acute reference dose
atm	atmosphere
ATPD	area treated per day
BAF	Bioaccumulation Factor
BALB	Bagg Albino inbred mouse strain
BCF	Bioconcentration Factor
BUN	blood urea nitrogen
bw	body weight
BW	Body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CD	Charles River Sprague-Dawley rats
CEPA	Canadian Environmental Protection Act
CHO/HGPRT	Chinese hamster ovary cell/hypozanthine-guanine phosphoribosyl-transferase
cm	centimetre(s)
cm^2	centimetre(s) squared
CO_2	carbon dioxide
d	day(s)
DAT	day(s) after treatment
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the time required to observe a 90% decline in concentration)
EC_3	concentration required to induce a stimulation index equal to 3
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration
ER_{50}	effective rate on 50% of the population
fc	food consumption
FIR	food ingestion rate
g	gram(s)
GD	gestation day(s)
GI	gastro-intestinal tract
GLP	good laboratory practice
GSD	geometric standard deviation

GUS	groundwater ubiquity score
h	hour(s)
ha	hectare(s)
HC/CFHB	outbred strain of rats of Wistar origin supplied by Hacking and Churchill
HC5	hazardous concentration 5%
HD	high dose
HDT	highest dose tested
Hg	mercury
iv	intravenous
K_d	soil-water partition coefficient
kg	kilogram(s)
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50%
LD	low dose
LD_{50}	lethal dose to 50%
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOC	level of concern
LR_{50}	lethal rate 50%
m^2	metre(s) squared
m^3	metre(s) cubed
MAS	maximum average score
mg	milligram(s)
MHE	methylheptyl ester
MIS	maximum irritation score
mL	millilitre(s)
MLA	mixer / loader / applicator
mm	millimetre(s)
MMAD	mass median aerodynamic diameter
MOE	margin of exposure
mPa	milliPascal(s)
N/A	not applicable
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NZW	New Zealand white
Pa	Pascal(s)
PGR	plant growth regulator
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RCB	randomized complete block
REI	restricted entry interval
rel	relative
RQ	risk quotient

SFO	single first order
SI	stimulation indice
SSD	species sensitivity distribution
$t_{1/2}$	half-life
TC	transfer coefficient
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet
μg	microgram(s)
μm	micrometre(s)
wt	weight
w/w	weight per weight

Appendix I Tables and Figures

Table 1 Toxicity Profile of Starane II Herbicide

Study type/ Animal	Study results[a]	Reference
Acute oral toxicity (Up and Down) Fischer 344 rats	LD_{50}♀ > 5000 mg/kg bw **Low toxicity**	1397957
Acute dermal toxicity Fischer 344 rats	LD_{50} > 5000 mg/kg bw **Low toxicity**	1397958
Acute inhalation toxicity (nose-only) Fischer 344 rats	LC_{50} > 5.5 mg/L **Low toxicity** MMAD: 2.4 µm GSD: 1.85	1397959
Dermal irritation NZW rabbits	$MIS_{(at\ 1h)}$ = 3.0/8 $MAS_{(at\ 24,\ 48\ and\ 72h)}$ = 1.43/8 **Mildly irritating**	1397961
Eye irritation NZW rabbits	$MAS_{(at\ 24h\ and\ 48h)}$ = 26.0/110 **Moderately irritating**	1397960
Dermal sensitization (LLNA method) BALB mice	Stimulation indices (SI) (fold vs. control): 2.3 (at 1.5%), 2.5 (5%) and 11.2 (25%) SI for the positive control: 17.7 EC_3: 6.2% **Potential Skin Sensitizer**	1397962

[a] Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons

Table 2 Toxicity Profile of Technical Fluroxypyr

Study type/ Animal	Study results[a]	Reference
Toxicokinetic Studies		
Biokinetics and metabolism CD rats	Biokinetics and distribution of oral doses of 50 mg/kg bw/day of ^{14}C labelled fluroxypyr MHE were studied in male and female CD rats. A single dose was rapidly and essentially completely absorbed, with peak plasma concentrations reached in 40 minutes (males 15.1 µg/mL) to two hours (females 24.9 µg/mL). Repeat doses for seven days produced similar plasma peaks with respect to both time and level. Distribution was mainly to the GI tract, blood and kidneys. There was no bioaccumulation. Over 90% of the administered dose was excreted in the urine within 24 hours (92.1% by day 6) and fluroxypyr acid accounted for almost all the urinary excreted radioactivity (> 93%). A less polar component made up the remaining 1-2% of radioactivity, with other radioactive components being present at less than 1%. No radioactivity was detected in expired air, (measured at 48 hours) but over the seven day time course, 5.6±0.4% was excreted in the faeces and 0.11% remained in the carcass. Biliary excretion was <1% within 48 hours following a single dose.	1144297
Pharmacokinetics Wistar rats	Single oral doses of 20 or 200 mg/kg bw or single jugular intravenous doses of 20 mg/kg bw of 2,6-^{14}C labelled fluroxypyr acid, administered to male Wistar rats (3/group) were rapidly and essentially completely absorbed. The time to peak plasma concentration was 30 minutes at the low dose and 90 minutes at the high dose. There was a saturation of absorption at the high dose while elimination was not affected by dose. The dose was efficiently eliminated in the urine (94±1.3% by 48 hours post dosing), unchanged, possibly by partial active secretion, through the kidney. A small amount was excreted via the faeces (4-5% of administered dose). Following iv administration only, a low level of ^{14}C activity (0.5%) remained in the skin (dorsal sample) at 24 hours. Following oral or iv dosing, there was no detectable residual tissue radioactivity by 48 hours.	1144301
Acute Toxicity Studies - TECHNICAL		
Acute oral toxicity (ester) Sprague-Dawley rats	Supplemental (range-finding) No deaths occurred at the highest dose of 5000 mg/kg bw. No treatment-related effects.	1144287
Acute oral toxicity (acid) Sprague-Dawley rats	LD_{50} > 2000 mg/kg bw **Low toxicity**	1144286
Acute dermal toxicity (acid) NZW rabbits	Supplemental No mortality or clinical signs of systemic toxicity at 5000 mg/kg bw.	1144286

Study type/ Animal	Study results[a]	Reference
Acute dermal toxicity (ester) Sprague-Dawley rats	LD_{50} > 2000 mg/kg bw **Low toxicity**	1144288
Acute inhalation toxicity (ester) (whole-body) HC/CFHB rats	LC_{50} > 1.0 mg/L **Slight toxicity** Proportion ≤ 5.5 µm was 56% Proportion ≤ 4 µm was 38.6%	1144289
Dermal irritation (acid) NZW rabbits	MAS = 0, MIS = 0 **Non-irritating**	1144286
Dermal irritation (ester) NZW rabbits	MAS = 0, MIS = 0 **Non-irritating**	1144269
Eye irritation (acid) NZW rabbits	MIS = 3.67/110 MAS = 3.11/110 Unresolved at the 72- hour reading **Mildly irritating**	1144286
Eye irritation (ester) NZW rabbits	MIS = 2.67/110 MAS = 0.89/110 **Minimally irritating**	1144290
Dermal sensitization (ester) (Buehler test) Hartley guinea pigs	**Non-sensitizer**	1144270
Short-Term Toxicity Studies		
21-Day dermal toxicity (ester) NZW rabbits	NOAEL = limit dose of 1000 mg/kg bw/day No dermal or systemic treatment-related adverse effect.	2065120
28-Day oral toxicity (diet) (acid) CD-1 mice	NOAEL = 13/1748 mg/kg bw/day (♂/♀) **≥ 135 mg/kg bw/day:** kidney tubule epithelial degeneration (♂) **3496 mg/kg bw/day:** kidney tubule epithelial degeneration and unilateral papillary degeneration (♀)	1126647

Study type/ Animal	Study results[a]	Reference
90-Day oral toxicity (diet) (acid) CD-1 mice	NOAEL = 1342/1748 mg/kg bw/day (♂/♀) No treatment-related effects	1126647
90-Day oral toxicity (diet) (acid) Wistar rats (supplemental)	**500 mg/kg bw/day:** ↑ incidence of slight tubular dilatation or cellular irregularity in tubules of outer medulla of kidneys (no examination of tissues at low and mid doses); ↑ALP activity (♂)	1144272
90-Day oral toxicity (diet) (acid) Fischer 344 rats	NOAEL = 1000 mg/kg bw/day **1000 mg/kg bw/day:** ↑ rel kidney wt; ↑ rel liver wt (♀) (*adaptive*) **Recovery groups** **1000 mg/kg bw/day:** still ↑ kidney wt (♂) (*adaptive*)	1126649
90-Day oral toxicity (diet) (acid) Wistar rats	NOAEL = 80/750 mg/kg bw/day (♂/♀) **750 mg/kg bw/day:** ↑ALP, ↓ plasma protein (♂) (no higher dose ♂ remaining, clinical chemistry not performed at higher doses) **≥750 mg/kg bw/day:** ↓bwg, ↓fc, poor general condition; mortality, papillary interstitial hypercellularity, cellular hypertrophy, urothelial hyperplasia of the kidney pelvis, cortical tubular degeneration, tubular dilatation, renal papillary necrosis, hypertrophy and/or degeneration of the adrenal zona glomerulosa , depletion of the red and white splenic pulp, involution of the thymus and atrophy of the seminal vesicles (♂) **≥1000 mg/kg bw/day:** mortality, renal papillary necrosis, hypertrophy and/or degeneration of the adrenal zona glomerulosa; ↓ plasma protein (♀) **12-week recovery:** abnormalities remained in the kidneys and adrenals. **24-week recovery:** kidneys were still affected, though less severely, and particularly in males.	1144273, 1162946
28-Day oral toxicity (dietary) (acid) (range-finding) Beagle dogs	First two weeks intake was approximately 300 mg/kg bw/day. Subsequently the 500 mg/kg bw dose was administered in capsule form. **150 mg/kg bw/day:** signs of early acute kidney tubular necrosis (slight to moderate), patchy coagulation necrosis of the proximal tubule. **300-500 mg/kg bw/day:** ↓ bw, ataxia, weakness of hind legs, ↓ potassium, ↓ calcium, ↑ cholesterol, ↑kidney wt, acute proximal renal tubular necrosis (moderate), acute irritation-related gastroenteritis; ↑ BUN, ↑ creatinine, ↑ uric acid, ↑bilirubin (♀)	1144274

Study type/ Animal	Study results[a]	Reference
1-Year oral toxicity (dietary) (acid) Beagle dogs	NOAEL = 150 mg/kg bw/day No treatment-related effects.	1144275
Chronic Toxicity/Oncogenicity Studies		
18-Month oncogenicity (diet) (acid) CD-1 mice	NOAEL = 101 mg/kg bw/day **≥302/306 mg/kg bw/day:** severe regenerative nephrosis; ↑ incidence of renal papillary necrosis (♂); incidences of ↓ kidney size (♀) **No evidence of oncogenicity**	1126652
24-Month chronic/ Oncogenicity (diet) (acid) Wistar rats	NOAEL = 80 mg/kg bw/day **≥320 mg/kg bw/day:** ↑ incidence and severity of kidney nephrosis, ↑ ALP @ 1 year **≥320 mg/kg bw/day:** bile duct stenosis (♂) **No evidence of oncogenicity**	1144276, 1126651, 1144278, 1144281, 1144282, 1144280, 1144277
24-Month chronic/ Oncogenicity (diet) (acid) Fischer 344 rats	NOAEL = 100 mg/kg bw/day **≥ 500 mg/kg bw/day:** ↑kidney wt, increasing severity of progressive glomerulonephropathy; papillary necrosis, pelvic epithelial hyperplasia and/or tubular nephrosis (♂) **No evidence of oncogenicity**	1160770, 1160771
Developmental/Reproductive Toxicity Studies		
2-Generation dietary reproductive toxicity (diet) (acid) Wistar rat	**Parental Toxicity** NOAEL = 472 mg/kg bw/day No treatment-related effects **Offspring Toxicity** NOAEL = 472 mg/kg bw/day No treatment-related effects **Reproductive Toxicity** NOAEL = 472 mg/kg bw/day No treatment-related effects. **No sensitivity of the young**	1144319, 1144320, 1126654

Study type/ Animal	Study results[a]	Reference
Developmental toxicity (gavage) (acid) Sprague-Dawley rats	Range-finding Mortality: 2♀ @ 1000 mg/kg bw/day (GD 13 and 15) **≥250 mg/kg bw/day:** ↑ salivation (severity and time of onset were dose-related), brown facial staining **≥ 500 mg/kg bw/day:** ↑ kidney wt **1000 mg/kg bw/day:** ↓ bwg	1144321, 1126655
Developmental toxicity (gavage) (acid) Sprague-Dawley rats	**Maternal** NOAEL = 250 mg/kg bw/day **500 mg/kg bw/day:** ↑ kidney wt, ↑ incidence of renal pelvic dilatation **Developmental** NOAEL = 250 mg/kg bw/day **500 mg/kg bw/day:** reduced ossification of sternebrae **No sensitivity of the young** **No evidence of teratogenicity**	1144321, 1126655
Developmental toxicity (gavage) (ester) Sprague-Dawley rats	**Maternal** NOAEL = 300 mg/kg bw/day **600 mg/kg bw/day:** ↓ bwg, reduced corrected bw change, ↓ fc, lethargy, hypothermia, laboured breathing, irregular gait, pale appearance. **Developmental** NOAEL = 300 mg/kg bw/day **600 mg/kg bw/day:** variations: ↑ incidence of incompletely ossified cervical vertebral transverse processes and incompletely ossified pubes **No sensitivity of the young** **No evidence of teratogenicity**	2065150
Developmental toxicity (range-finding) (gavage) (acid) NZW rabbits	Mortality: 2♀ died @ 1000 mg/kg/day prior to scheduled necropsy and this group was terminated. **Maternal** **≥500 mg/kg bw/day:** ↑ respiration rate, muscular weakness, incoordination **Developmental** **500 mg/kg bw/day:** ↓ foetal and placental wt	2065157

Study type/ Animal	Study results[a]	Reference
Developmental toxicity (gavage) (acid) NZW rabbits	**Maternal** NOAEL = 250 mg/kg bw/day **400 mg/kg bw/day:** ↑ respiration, ataxia, muscular weakness, group terminated on Day 9 **Developmental** NOAEL = 250 mg/kg bw/day (HDT) No treatment-related effects **No evidence of malformations**	1144322, 1144323
Developmental toxicity (range-finding) (gavage) (ester) NZW rabbits	**Maternal** No treatment-related effects **Developmental** No treatment-related effects	2065157
Developmental toxicity (gavage) (ester) NZW rabbits	**Maternal** NOAEL = 500 mg/kg bw/day **1000 mg/kg bw/day:** ↓ fc, ↓ bw, abortions **Developmental** NOAEL = 100 mg/kg bw/day **≥ 500 mg/kg bw/day:** ↑ incidence variations (retrocaval ureter) **Sensitivity of the young** **No evidence of teratogenicity**	2065157
Genotoxicity Studies		
Gene mutation in bacteria (acid) *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98, TA100)	Negative	1144324
Gene mutation in bacteria (ester) *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98, TA100)	Negative	2065164

Study type/ Animal	Study results[a]	Reference
Gene mutation in mammalian cells *in vitro* (acid) CHO/HGPRT-locus	Negative	1144292
Gene mutation in mammalian cells *in vitro* (ester) CHO/HGPRT-locus	Negative	2065170, 2138893
Chromosome aberration *in vitro* (acid) CHO cells	Negative	1144293
Chromosome aberration *in vitro* (ester) Sprague-Dawley rat lymphocytes	Negative	2065166
Unscheduled DNA synthesis *in vivo* (acid) Human embryonic lung cells	Negative	1144294
In vivo mammalian micronucleus assay (ester) CD-1 mice	Negative	2065169
Chromosome aberration *in vivo* (ester) Chinese hamsters	Negative	2065171

[a] Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Fluroxypyr

Exposure scenario	Study	Point of departure and endpoint	CAF[a] or target MOE
Acute dietary general population		No acute toxicity endpoint was identified	
	ARfD = N/A		
Repeated dietary	2-year rat chronic toxicity/oncogenicity	NOAEL = 100 mg/kg bw/day Kidney nephrosis	100
	ADI = 1 mg/kg bw/day		
Short and Intermediate term dermal	21-day dermal study in rabbits	NOAEL = 1000 mg/kg bw/day Absence of adverse effects at the highest dose tested	100
Short and Intermediate term inhalation	2-year rat chronic toxicity/oncogenicity[b]	NOAEL = 100 mg/kg bw/day Kidney nephrosis	100
Aggregate	N/A		
Cancer	N/A		

[a] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments

[b] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 4 PHED unit exposure estimates for mixer/loader and applicators while handling Starane II Herbicide

Scenario		Dermal[a] (µg/kg ai handled)	Inhalation[b] (µg/kg ai handled)
Mixer/loader PHED estimates			
A	All liquids, open mixing/loading (coveralls over single layer, gloves)	32.77	1.60
Applicator PHED estimates			
B	Broadcast sprayer (coveralls over single layer, gloves)	524.07	5.00
Mixer/loader + applicator PHED estimates			
A+B	MLA Broadcast (coveralls over single layer, gloves)	556.84	6.60
C	Liquid/Open pour/Low pressure handwand (coveralls over single layer, gloves)	735.22	45.2
D	Liquid/open pour/backpack (coveralls over single layer, gloves)	2597.09	62.1
E	Liquid/open pour/high pressure handwand (coveralls over single layer, gloves)	2453.52	151.00

MLA = mixer/loader/applicator

[a] Not adjusted with dermal absorption factor, since dermal NOAEL is based on dermal toxicity study

[b] Light inhalation rate, except for backpack, which used moderate inhalation rate

Table 5 Chemical handler risk assessment for Starane II Herbicide

Exposure scenario	PHED unit exposure (µg/kg a.i. handled)[a]		ATPD[b]	Rate	Daily exposure (mg/kg bw/day)[c]		MOE [d]	
	Dermal	Inhalation			Dermal	Inhalation	Dermal	Inhalation
PPE: Coveralls over single layer and gloves								
MLA Broadcast sprayer	556.84	6.6	3800 L/day	0.00028 kg ai/L	8.46E-03	1.00E-04	118000	997000
MLA Low pressure handwand	735.22	45.2	150 L/day	0.00028 kg ai/L	4.41E-04	2.71E-05	2270000	3690000
MLA Liquid/open pour/backpack	2597.1	62.1	150 L/day	0.00028 kg ai/L	1.56E-03	3.73E-05	642000	2680000
MLA Liquid/open pour/high pressure handwand	2453.5	151	3800 L/day	0.00028 kg ai/L	3.73E-02	2.30E-03	26800	43600

MLA = mixer/loader/applicator; PHED = Pesticide Handlers Exposure Database; MOE = margin of exposure, ATPD = area treated per day

[a] PHED unit exposures from Table 4

[b] Default values

[c] Daily exposure = (PHED unit exposure x ATPD x Rate) / (70 kg bw x 1000 µg/mg)

[d] Dermal: based on NOAEL = 1000 mg/kg bw/day, target MOE = 100
Inhalation: based on NOAEL = 100 mg/kg bw/day, target MOE = 100

Table 6 Postapplication exposure and risk estimate for non-crop areas treated with Starane II Herbicide

Re-entry activity	Peak DFR ($\mu g/cm^2$)[a]	Transfer Coefficient (cm^2/h)[b]	Dermal Exposure (mg/kg bw/day)[c]	MOE[d]	REI
Scouting, mechanical weeding, mowing in minimal foliage	0.560	500	0.0320	31300	Until residues are dried
Scouting, mechanical weeding, mowing in full foliage	0.560	1500	0.0960	10400	Until residues are dried

DFR = dislodgeable foliar residue; MOE = margin of exposure; REI = restricted entry interval

[a] Calculated using the default 20% of the application rate dislodgeable on the day of application

[b] Transfer coefficients obtained from USEPA Policy 3.1

[c] Exposure = (Peak DFR [$\mu g/cm^2$] × TC [cm^2/h] × 8 hours) / (70 kg bw × 1000 µg/mg); not adjusted with dermal absorption factor, since dermal NOAEL is based on dermal toxicity study

[d] Based on a NOAEL of 1000 mg/kg bw/day, target MOE = 100

Table 7 Toxic Substances Management Policy considerations - Comparison to TSMP Track 1 criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints		Transformation Products (TP) Endpoints
			Fluroxypyr-methyl heptyl ester	Fluroxypy acid	
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	$t_{1/2}$ of 0.3 to 1.8 days	$t_{1/2}$ of 2.9 to 82.5 days (ester + acid)	$t_{1/2}$ of 3.1 to 85.2 days (pyridinol); $t_{1/2}$ of 16.7 to > 1000 days (methoxypyridine)
	Water	Half-life ≥ 182 days	$t_{1/2}$ of 31.3 to 38.1 days in water-sediment systems	Not available	Not available
	Sediment	Half-life ≥ 365 days	Not available	Not available	Not available
	Air	Half-life ≥ 2 days or evidence of long range transport	Volatilisation is not expected and long-range atmospheric transport is unlikely to occur based on the vapour pressure (3.5×10^{-8} mm Hg at 20°C) and Henry's Law Constant (1.55×10^{-7} atm·m^3/mol at 20°C).	Volatilisation is not expected and long-range atmospheric transport is unlikely to occur based on the vapour pressure (8.12×10^{-11} mm Hg at 20°C) and Henry's Law Constant (3.42×10^{-15} atm·m^3/mol at 20°C).	Not available
Bioaccumulation[4]	Log K_{OW} ≥ 5		Log K_{OW} = 4.53 – 5.31	Not available	Log K_{OW} = 3.09 (methoxypyridine)
	BCF ≥ 5000		BCF = 26	Not available	Not available
	BAF ≥ 5000		Not available	Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.	No, do not meet TSMP Track 1 criteria.

[1] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log KOW).

Table 8 Fate and behaviour in the environment

Property	Test substance	Value	Transformation products (major)	Comments	PMRA
Abiotic transformation					
Hydrolysis	Fluroxypyr-MHE[a] (Sterile buffered)	pH 5: stable pH 7: stable pH 9: t½ 3.2 d	Fluroxypyr acid (stable)	Major route of transformation under alkaline conditions or when highly diluted; stable at neutral and acid conditions	1144311
	Fluroxypyr-MHE (Highly diluted solutions)	$t_{½}$ = 12.8-16.5 h (not pH dependent)	Fluroxypyr acid		2100408
	Fluroxypyr acid	$t_{½}$ > 200 d (pH 5-9)	None		2100408
Phototransformation in water	2,6 [^{14}C]-labelled fluroxypyr-MHE	Stable (t½ = 210 d)	None	Not major route of transformation in the environment	2100408
	2,6 [^{14}C]-labelled fluroxypyr acid	Stable (t½ = 365 d)	None		1162912
Phototransformation on soil	Fluroxypyr-MHE	stable	None	Not major route of transformation in the environment	1139212
Biotransformation					
Biotransformation in aerobic soil	Fluroxypyr-MHE	$t_{½}$: 0.3 - 1.8 d (SFO)	Fluroxypyr acid Pyridinol Methoxypyridine	Non-persistent	2065217 1144705 1484999 2100408
	Fluroxypyr (ester + acid)	$t_{½}$: 2.9 – 82.5 d (SFO) DT_{90}: 9.6 – 274.1 d (SFO)	Pyridinol Methoxypyridine	Non-persistent to moderately persistent	2065217 1144705 1484999 2100408
	Pyridinol	$t_{½}$: 3.1 – 85.2 d (SFO) DT_{90}: 10.3– 283.0 d (SFO)	NA[b]	Non-persistent to moderately persistent	2065217 1144705 1484999 2100408
	Methoxypyridine	$t_{½}$: 16.7 – >1000 d (SFO) DT_{90}: 55.5 – >3322 d (SFO)	NA	Persistent	2065217 1144705 1484999 2100408
Biotransformation in anaerobic soil	Fluroxypyr (ester +acid)	$t_{½}$: 91 - 210 d	Pyridinol Methoxypyridine	moderately persistent to persistent	2100408
Biotransformation in aerobic sediment -water systems	2,6 [^{14}C]-labelled fluroxypyr-MHE	$t_{½}$ = 7- 14 d	Pyridinol / pyridinone 3-chloropyridinol	Non-persistent	1162912
	2,6 [^{14}C]-labelled fluroxypyr-MHE	$t_{½}$ = 31.3 -38.1 d DT_{90} = 103.9 – 126.5 d		Slightly persistent	2100408
	Pyridinol + pyridinone	$t_{½}$ = 27.8 -35.5 d DT_{90} = 92.3 – 118 d	CO_2	Slightly persistent	2100408
Biotransformation in anaerobic sediment-water systems	2,6 [^{14}C]-labelled fluroxypyr-MHE	$t_{½}$ = 7- 14 d	Pyridinol / pyridinone 3-chloropyridinol	Non-persistent	1162912 2065221

Property	Test substance	Value	Transformation products (major)	Comments	PMRA
Mobility					
Adsorption / desorption in soil	Fluroxypyr MHE	K_d: 95-260 mL/g; K_{oc}: 6200 - 43000 mL/g		Immobile	1139217 1144317 1162910 1162911 2100408
	Fluroxypyr acid	K_d: 0.78-1.34 mL/g; K_{oc}: 32.6-71 mL/g		Highly mobile	
	Pyridinol	K_d: 1.05-2.0 mL/g; K_{oc}: 36.5-99.8 mL/g		Highly mobile	
	Methoxypyridine	K_d: 9.71-13.43 mL/g; K_{oc}: 373.5-516.7 mL/g		Moderately mobile	
Soil column leaching	Fluroxypyr acid	5 to 15% of added acid present in the leacheate; pyridinol not detected in leacheate		Low to moderate mobility	1484999
Partitioning					
Adsorption / desorption in sediment	2,6 [^{14}C]-labelled fluroxypyr-MHE	Increased in sediment up to 50% of applied in 2 hours	N/A	Partitions into sediment	2100408
Bioconcentration/Bioaccumulation					
Bioconcentration	2,6 [^{14}C]-labelled fluroxypyr-MHE	BCF = 26 (fluroxypyr-MHE) BCF = 167 (total ^{14}C activity)	< 5% of the total ^{14}C activity	Fluroxypyr acid accounted for 80 – 90 % of the total ^{14}C activity	1166925
Field studies					
Field dissipation	Fluroxypyr (ester +acid)	$t_{½}$: 13.2 – 36.3 d	Pyridinol Methoxypyridine	Slightly persistent	1863385
Field leaching	Fluroxypyr (ester +acid) Pyridinol Methoxypyridine	Mostly detected in the top 15 cm soil depth. No residues beyond 45 cm soil depth		Low leaching potential	1863385

[a]Fluroxypyr-MHE: Fluroxypyr-methyl heptyl ester ; [b]N/A: not applicable

Table 9 Effects on terrestrial organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Invertebrates					
Earthworm (*Eisenia foetida*)	14-day Acute	Fluroxypyr-MHE	LC_{50} > 1000 mg a.i./kg dry soil	No classification	2100405
		Fluroxypyr acid	LC_{50} = 64.8 mg a.e./kg dry soil		2100405
		Pyridinol	LC_{50} = 79 mg /kg dry soil		2100405
		Methoxypyridine	LC_{50} = 313 mg/kg dry soil		2100405 1166926
Bee (*Apis mellifera*)	Oral	Fluroxypyr-MHE	LD_{50}>100 µg a.i./bee	Relatively non toxic	2100405 1144723
	Oral	Fluroxypyr acid	LD_{50} = 37.1 µg a.e./bee		2100405
	Contact	Fluroxypyr-MHE	LD_{50} > 100 µg a.i./bee		2100405
	Contact	Fluroxypyr acid	LD_{50} > 180 µg a.e./bee		2100405
Predatory mite (*Typhlodromus pyri*)	7-day Contact (glass plates)	Starane 180 EC	LR_{50} > 2200 mL product/ha, or LR_{50} > 570 g a.i./ha	No classification	2100405
Parasitic wasp (*Aphidius rhopalosiphi*)	48-hour Contact (glass plates)	Starane 180 EC	LR_{50} = 1301 mL product/ha, or LR_{50} = 337 g a.i./ha		2100405

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Birds					
Bobwhite quail (*Colinus viriginianus*)	Acute oral	Fluroxypyr-MHE	LD_{50} > 2000 mg a.i./kg bw/d	Practically non toxic	2100405 1144763
	Acute oral	Fluroxypyr acid	LD_{50} > 2000 mg a.e./kg bw/d		2100405 1144760
	8-day Dietary	Fluroxypyr-MHE	LC_{50} > 5000 ppm LD_{50} > 1036 mg a.i./kg bw/d	Practically non toxic	2100405 1144765
	8-day Dietary	Fluroxypyr acid	LC_{50} > 5000 ppm LD_{50} > 757.1 mg a.e./kg bw/d		2100405 1144764
	19-week Reproduction	Fluroxypyr-MHE	NOEC = 500 ppm	No classification	1144706
Mallard duck (*Anas platyrhynchos*)	Acute oral	Fluroxypyr- MHE	LD_{50} > 2000 mg a.i./kg bw	Practically non toxic	1144749
	Acute oral	Fluroxypyr acid	LD_{50} > 2000 mg a.e./kg bw		1144738
	8-day Dietary	Fluroxypyr acid	LC_{50} > 5620 ppm	Practically non toxic	2065270
	18-week Reproduction	Fluroxypyr-MHE	NOEC = 500 ppm NOEL = 57.8 mg a.i./kg bw/d	No classification	2100405 1144707
	18-week Reproduction	Fluroxypyr acid	NOEL = 40.1 mg a.e./kg bw/d		2100405
Mammals					
Rat	Acute	Fluroxypyr-MHE	LD_{50} > 2000 mg a.i./kg bw/d	Practically non toxic	2100405
	Reproduction	Fluroxypyr acid	NOAEL = 250 mg a.e./kg bw/d (teratogenicity)	No classification	2100405
Vascular plants					
Carrot	Post-emergence phytotoxicity	Fluroxypyr-MHE	EC_{50} = 119.7 g. a.i./ha	No classification	1166928 1485003
Cotton			EC_{50} = 5.47 g. a.i./ha		
Cucumber			EC_{50} = 69.7 g. a.i./ha		
Bean			EC_{50} = 41.6 g. a.i./ha		
Radish			EC_{50} = 191.7 g. a.i./ha		
Soybean			EC_{50} = 36.6 g. a.i./ha		
Sunflower			EC_{50} = 14.8 g. a.i./ha		
Tomato			EC_{50} = 5.52 g. a.i./ha		
Corn			EC_{50} > 560 g. a.i./ha		
HC_5 of SSD of EC_{50}: 3.00 g a.i./ha (phytotoxicity)					2158132

[a] Atkins et *al.*(1981) for bees and USEPA classification for others, where applicable

Table 10 Effects on aquatic organisms

Test organism	Test condition	Test, duration	End point (mg/L)	Degre of toxicity	PMRA
Fluroxypyr-MHE					
Rainbow trout *Oncorhynchus mykiss*	Static renewal	Acute, 96-h	$LC_{50} > 0.2$*	No effect at solubility limit	2100405
	Flow-through	Chronic, 21-d	NOEC = 0.2*	No classification	2100405
	Flow-through	Bioconcentration, 28-d uptake + 17-d depuration	BCF = 26	No classification	1166925 1485003
Waterflea *Daphnia magna*	Static renewal	Acute, 48-h	$EC_{50} > 0.2$*	No effect at solubility limit	2100405
	Flow-through	Chronic, 21-d	NOEC = 0.0605	No classification	2100405
Duckweed *Lemna gibba*	Static	Chronic, 14-d	$EC_{50} > 2.31$	No classification	2100405 2065284
Midge *Chironomus riparius*	Static	Chronic, 28-d	NOEC = 0.13	No classification	2100405
Diatom (marine) *Skeletonema costatum*	Static	Chronic, 120-h	$EC_{50} = 0.208$	No classification	2100405
Green alga *Scenedesmus subspicatus*	Static	Chronic, 96-h	$EC_{50} > 0.5$	No classification	2100405
Blue-green alga *Anabaena flos-aqua*	Static	Chronic, 120-h	$EC_{50} = 0.395$	No classification	2100405
Diatom (freshwater) *Navicular pellicullosa*	Static	120-h	$EC_{50} = 0.037$	No classification	2065294
Fluroxypyr acid					
Bluegill sunfish *Lepomis macrochirus*	Static	Acute, 96-h	$LC_{50} = 14.3$	Slightly toxic	2100405
Rainbow trout *Oncorhynchus mykiss*	Semi-static	Chronic, 21-d	NOEC = 100	No classification	2100405 1144709
Waterflea *Daphnia magna*	Static	Acute, 48-h	$EC_{50} > 100$	At worst, slightly toxic	2100405 1144711
	Semi-static	Chronic, 21-d	NOEC = 56	No classification	1144720
Green alga *Selenastrum capricornutum*	Static	Chronic, 120-h	$EC_{50} = 49.8$ (biomass)	No classification	2100405

Test organism	Test condition	Test, duration	End point (mg/L)	Degre of toxicity	PMRA
Duckweed *Lemna gibba*	Static	Chronic, 14-d	EC_{50} = 12.3 (frond number)	No classification	2100405
Diatom (freshwater) *Navicular pellicullosa*	Static	Chronic, 96-h	EC_{50} = 26 (biomass)	No classification	2100405
Fluroxypyr pyridinol					
Rainbow trout *Oncorhynchus mykiss*	Semi-static	Acute, 96-h	LC_{50} = 39	At worst, slightly toxic	2100405
Waterflea *Daphnia magna*	Static	Acute, 48-h	EC_{50} > 49	At worst, slightly toxic	2100405
Green alga *Selenastrum capricornutum*	Static	Chronic, 96-h	EC_{50} > 45	No classification	2100405
Blue-green alga *Anabaena flos-aqua*	Static	Chronic, 120-h	EC_{50} > 2.9	No classification	2100405
Diatom (freshwater) *Navicular pellicullosa*	Static	Chronic, 120-h	72 h EC_{50} = 0.640	No classification	2100405
Diatom (marine) *Skeletonema costatum*	Static	Chronic, 120-h	EC_{50} > 3.0	No classification	2100405
Duckweed *Lemna gibba*	Static	Chronic, 14-d	EC_{50} > 3.2	No classification	2100405
Fluroxypyr methoxypyridine					
Blue-green alga *Anabaena flos-aqua*	Static	Chronic, 120-h	96 h EC_{50} = 1.19	No classification	2100405
Diatom (freshwater) *Navicular pellicullosa*	Static	Chronic, 120-h	EC_{50} = 3.37	No classification	2100405
Diatom (marine) *Skeletonema costatum*	Static	Chronic, 120-h	EC_{50} = 7.82	No classification	2100405
Duckweed *Lemna gibba*	Static	Chronic, 14-d	EC_{50} = 10.6	No classification	2100405

[a] limit of water solubility: is 0.109 mg/L

Table 11 Endpoints considered in the risk assessment

Organism	Test substance	Exposure	Endpoint	Value	Uncertainty factor applied
Earthworm (*Eisenia fetida*)	Fluroxypyr-MHE	Acute	14-d LC_{50}	> 1000 mg a.i./kg dry soil	2
	Fluroxypyr acid	Acute	14-d LC_{50}	64.8 mg /kg dry soil	2
	Pyridinol	Acute	14-d LC_{50}	79 mg /kg dry soil	2
	Methoxypyridine	Acute	14-d LC_{50}	313 mg /kg dry soil	2
Bee (*Apis mellifera*)	Fluroxypyr-MHE	Acute contact and acute oral	48-h LD_{50}	>100 µg a.i./bee	1
	Fluroxypyr acid	Acute contact and acute oral	48-h LD_{50}	37.1 µg /bee	1
Beneficial Insects (*Aphidius rhopalosiphi*)	Fluroxypyr-MHE	Contact	48-h LR_{50}	337 g a.i./ha	1
Birds, Bobwhite quail (*Colinus viriginianus*)	Fluroxypyr-MHE	Acute oral	LD_{50}	>2000 mg a.i /kg bw/d	10
	Fluroxypyr acid	Acute dietary	LD_{50}	757.1 mg/kg bw/d	10
Birds, Mallard duck (*Anas platyrhynchos*)	Fluroxypyr-MHE	Chronic	NOEL (NOEC converted to dose)	57.8 mg a.i /kg bw/d	1
	Fluroxypyr acid	Reproduction	18-w NOEL (NOEC converted to dose)	40.1 mg/kg bw/d	1
Mammals, Rat	Fluroxypyr-MHE	Acute	LD_{50}	>2000 mg a.i./kg bw/d	10
Mammals, Rat	Fluroxypyr acid	Reproduction	NOEL (NOEC converted to dose)	250 mg/kg bw/d	1
Terrestrial vascular plants	Fluroxypyr-MHE	Post-emergence phytotoxicity	HC_5 of SSD of EC_{50}	3.00 g a.i./ha	1
Freshwater invertebrates (*Daphnia magna*)	Fluroxypyr-MHE	Acute	96-h EC_{50}	> 0.2 mg a.i./L	2
	Fluroxypyr acid	Acute	48-h EC_{50}	> 100 mg/L	2
	Pyridinol	Acute	48-h EC_{50}	> 49 mg/L	2
	Fluroxypyr-MHE	Chronic	21-d NOEC	0.0605 mg a.i./L	1
	Fluroxypyr acid	Chronic	21-d NOEC	56 mg/L	1
Freshwater fish, Rainbow trout (*Oncorhynchus mykiss*)	Fluroxypyr-MHE	Acute	96-h LC_{50}	> 0.2 mg a.i./L	10
	Pyridinol	Acute	96-h LC_{50}	39 mg/L	10
	Fluroxypyr-MHE	Chronic	21-d NOEC	0.2 mg a.i./L	1
	Fluroxypyr acid	Chronic	21-d NOEC	100 mg/L	1
Freshwater fish, Bluegill sunfish (*Lepomis macrochirus*)	Fluroxypyr acid	Acute	96-h LC_{50}	14.3 mg/L	10

Organism	Test substance	Exposure	Endpoint	Value	Uncertainty factor applied
Amphibians (fish data as surrogate)	Fluroxypyr-MHE	Acute	96-h LC_{50}	> 0.2 mg a.i./L	10
	Fluroxypyr acid	Acute	96-h LC_{50}	14.3 mg/L	10
	Pyridinol	Acute	96-h LC_{50}	39 mg/L	10
	Fluroxypyr-MHE	Chronic	21-d NOEC	0.2 mg a.i./L	1
	Fluroxypyr acid	Chronic	21-d NOEC	100 mg/L	1
Aquatic vascular plants, *Lemna gibba*	Fluroxypyr-MHE		14-d EC_{50}	> 2.31 mg a.i./L	2
	Fluroxypyr acid		14-d EC_{50}	12.3 mg/L	2
	Pyridinol		14-d EC_{50}	> 3.2 mg/L	2
	Methoxypyridine		14-d EC_{50}	1.19 mg/L	2
Algae, *Navicular pellicullosa*	Fluroxypyr-MHE		120-h EC_{50}	0.037 mg a.i./L	2
	Fluroxypyr acid		96-h EC_{50}	26 mg/L	2
	Pyridinol		72-h EC_{50}	0.640 mg/L	2
Algae, *Anabaena flos-aqua*	Methoxypyridine		96-h EC_{50}	3.37 mg/L	2
Saltwater algae, *Skeletonema costatum*	Fluroxypyr-MHE		120-h EC_{50}	0.208 mg a.i./L	2
	Pyridinol		120-h EC_{50}	> 3 mg/L	2
	Methoxypyridine		120-h EC_{50}	7.82 mg/L	2

Table 12 Screening level risk assessment on non-target species other than birds and mammals

Organism	Exposure	Endpoint value	EEC	RQ[a]	LOC exceeded
Invertebrates					
Earthworm	Acute	Fluroxypyr-MHE: LC_{50} > 1000 mg a.i./kg dry soil	0.18 mg a.i./kg dry soil	< 0.0036	No
		Fluroxypyr acid: LC_{50} = 64.8 mg a.e./kg dry soil	0.12 mg a.e./kg dry soil	0.037	
		Pyridinol: LC_{50} = 79 mg/kg dry soil	0.1 mg /kg dry soil	0.026	
		Methoxypyridine: LC_{50} = 313 mg/kg dry soil	0.1 mg /kg dry soil	0.0006	
Bee	Oral	Fluroxypyr-MHE: LD_{50} >100 µg a.i./bee Or LD_{50} > 112 kg a.i./ha[b]	0.404 kg a.i./ha	< 0.0036	No
		Fluroxypyr acid: LD_{50} = 37.1 µg a.e./bee Or LD_{50} = 41.5 kg a.e./ha	0.280 kg a.e./ha	0.0067	
	Contact	Fluroxypyr-MHE: LD_{50} > 100 µg a.i./bee Or LD_{50} > 112 kg a.i./ha	0.404 kg a.i./ha	< 0.0036	No
		Fluroxypyr acid: LD_{50} > 180 µg a.e./bee Or LD_{50} > 201.6 kg a.i./ha	0.280 kg a.e./ha	< 0.0014	
Parasitic arthropod	Contact	LR_{50} = 337 g a.i./ha	404 g a.i./ha	1.2	No

Organism	Exposure	Endpoint value	EEC	RQ[a]	LOC exceeded
Vascular plants					
Vascular plant	Post-emergence phytotoxicity	HC_5 of SSD of EC_{50}: 3.00 g a.i./ha	404 g a.i./ha	135	Yes
Freshwater species					
Daphnia magna	Acute	Fluroxypyr-MHE: EC_{50} > 0.2 mg a.i./L	0.05 mg a.i./L	< 0.5	No
		Fluroxypyr acid: EC_{50} > 100 mg/L	0.035 mg a.i./L	< 0.0006	
		Pyridinol: EC_{50} > 49 mg/L	0.027 mg a.i./L	< 0.0005	
	Chronic	Fluroxypyr-MHE: NOEC: 0.0605 mg a.i./L	0.05 mg a.i./L	0.8264	No
		Fluroxypyr acid: NOEC: 56 mg/L	0.035 mg a.i./L	0.0006	
Rainbow trout	Acute	Fluroxypyr-MHE: LC_{50} > 0.2 mg a.i./L	0.05 mg a.i./L	< 2.5	Yes
		Pyridinol: LC_{50}: 39 mg/L	0.027 mg a.i./L	0.014	No
	Chronic	Fluroxypyr-MHE: NOEC: 0.2 mg a.i./L	0.05 mg a.i./L	0.25	
		Fluroxypyr acid: NOEC: 100 mg/L	0.035 mg a.i./L	0.0003	
Bluegill sunfish	Acute	Fluroxypyr acid LC_{50}: 14.3 mg/L	0.035 mg a.i./L	0.02	
Amphibians (fish data as surrogate)	Acute	Fluroxypyr -MHE: LC_{50} > 0.2 mg a.i./L	0.27 mg a.i./L	< 13.5	Yes
		Fluroxypyr acid: LC_{50}: 14.3 mg/L	0.19 mg a.i./L	0.13	No
		Pyridinol: LC_{50} = 39 mg/L	0.145 mg a.i./L	0.04	
	Chronic	Fluroxypyr-MHE: NOEC: 0.2 mg a.i./L	0.27 mg a.i./L	1.35	Yes
		Fluroxypyr acid: NOEC: 100 mg/L	0.19 mg a.i./L	0.002	No
Freshwater algae		Fluroxypyr-MHE: EC_{50}: 0.037 mg a.i./L	0.05 mg a.i./L	2.7	Yes
		Fluroxypyr acid: EC_{50}: 26 mg/L	0.035 mg a.i./L	0.0026	No
		Pyridinol: EC_{50}: 0.640 mg/L	0.027 mg a.i./L	0.0084	
		Methoxypyridine: EC_{50}: 3.37 mg/L	0.029 mg a.i./L	0.0172	

Organism	Exposure	Endpoint value	EEC	RQ[a]	LOC exceeded
Vascular plant	Dissolved	Fluroxypyr-MHE: EC_{50} > 2.31 mg a.i./L	0.05 mg a.i./L	<0.00432	
		Fluroxypyr acid: EC_{50}: 12.3 mg/L	0.035 mg a.i./L	0.0056	
		Pyridinol: EC_{50} > 3.2 mg/L	0.027 mg a.i./L	< 0.0168	
		Methoxypyridine: EC_{50}: 1.19 mg/L	0.029 mg a.i./L	0.0048	
Marine species					
Marine alga		Fluroxypyr-MHE: EC_{50}: 0.208 mg a.i./L	0.05 mg a.i./L	0.48	No
		Pyridinol: EC_{50} > 3 mg/L	0.027 mg a.i./L	< 0.018	
		Methoxypyridine: EC_{50}: 7.82 mg/L	0.029 mg a.i./L	0.0074	

[a] RQ = exposure/toxicity endpoint/uncertainity factor.

[b] According to Atkins *et al.* (1981), the LD_{50} in micrograms per bee (µg/bee) can be converted to the equivalent application rate in kg/ha by multiplying µg/bee by 1.12.

Table 13 Screening level risk assessment for birds and mammals exposed to fluroxypyr-MHE

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)[a]	RQ	LOC exceeded
Small Bird (20 g)					
Acute	200.00	Insectivore (small insects)	20.36	0.10	No
Reproduction	57.80	Insectivore (small insects)	20.36	0.35	
Medium Sized Bird (100 g)					
Acute	200.00	Insectivore (small insects)	15.89	0.08	No
Reproduction	57.80	Insectivore (small insects)	15.89	0.27	
Large Sized Bird (1 000 g)					
Acute	200.00	Herbivore (short grass)	16.58	0.08	No
Reproduction	57.80	Herbivore (short grass)	16.58	0.29	
Small Mammals (15 g)					
Acute	200.00	Insectivore (small insects)	11.71	0.06	No

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)[a]	RQ	LOC exceeded
Medium Sized Mammals (35 g)					
Acute	200.00	Herbivore (short grass)	36.68	0.18	No
Large Sized Mammals (1 000 g)					
Acute	200.00	Herbivore (short grass)	19.60	0.10	No

[a] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) x EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = 0.398(BW in g)$^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g)$^{0.651}$.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(BW in g)$^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

Table 14 Screening level risk assessment for birds and mammals exposed to fluroxypyr-acid

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)[a]	RQ	LOC exceeded
Small Bird (20 g)					
Acute	200.00	Insectivore (small insects)	14.11	0.07	No
Reproduction	40.10	Insectivore (small insects)	14.11	0.35	
Medium Sized Bird (100 g)					
Acute	200.00	Insectivore (small insects)	11.01	0.06	No
Reproduction	40.10	Insectivore (small insects)	11.01	0.27	
Large Sized Bird (1000 g)					
Acute	200.00	Herbivore (short grass)	11.49	0.06	No
Reproduction	40.10	Herbivore (short grass)	11.49	0.29	
Small mammal (15 g)					
Reproduction	250	Insectivore (small insects)	8.11	0.03	No
Medium Sized Mammals (35 g)					
Reproduction	250	Herbivore (short grass)	25.42	0.10	No

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)[a]	RQ	LOC exceeded
Large Sized Mammals (1000 g)					
Reproduction	250	Herbivore (short grass)	13.59	0.05	No

[a] EDE = Estimated dietary exposure, is calculated using the following formula: (FIR/BW) x EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = $0.398(BW \text{ in g})^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = $0.648(BW \text{ in g})^{0.651}$.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(BW \text{ in g})^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

Table 15 Refined risk assessment on non-target species based on spray drift

Organism	Exposure	Endpoint value	Refined EEC (mg a.i./L)	RQ	Level of Concern
Amphibians (fish data as surrogate)	Acute	Fluroxypyr-MHE: $LC_{50} > 0.2$ mg a.i./L	Ground application: (3% drift): 0.008	< 0. 4	No
	Chronic	Fluroxypyr-MHE: NOEC: 0.2 mg a.i./L	Ground application: (3% drift): 0.008	0.04	No
Rainbow trout	Acute	Fluroxypyr-MHE: $LC_{50} > 0.2$ mg a.i./L	Ground application: (3% drift): 0.0015	0.07	No
Freshwater alga		Fluroxypyr-MHE: EC_{50}: 0.037 mg a.i./L	Ground application: (3% drift): 0.0015	0.08	No
Terrestrial Vascular plant	Post-emergence phytotoxicity	HC_5 of SSD of EC_{50}: 3.00 g a.i./ha	Off-field (3% of ground application: 12.12 g a.i./ha	4.04	Yes

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B. Additional Information Considered

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